

Recommendations

- 1- Allergic rhinitis is a major chronic respiratory disease due to its:
 - prevalence,
 - impact on quality of life,
 - impact on work/school performance and productivity,
 - economic burden,
 - links with asthma.
- 2- In addition, allergic rhinitis is associated with sinusitis and other co-morbidities such as conjunctivitis.
- 3- Allergic rhinitis should be considered as a risk factor for asthma along with other known risk factors.
- 4- A new subdivision of allergic rhinitis has been proposed:
 - intermittent
 - persistent
- 5- The severity of allergic rhinitis has been classified as "mild" and "moderate/severe" depending on the severity of symptoms and quality of life outcomes.
- 6- Depending on the subdivision and severity of allergic rhinitis, a stepwise therapeutic approach has been proposed.
- 7- The treatment of allergic rhinitis combines:
 - allergen avoidance (when possible),
 - pharmacotherapy,
 - immunotherapy.
- 8- The environmental and social factors should be optimised to allow the patient to lead a normal life.
- 9- Patients with persistent allergic rhinitis should be evaluated for asthma by history, chest examination and, if possible and when necessary, the assessment of airflow obstruction before and after bronchodilator.
- 10- Patients with asthma should be appropriately evaluated (history and physical examination) for rhinitis.
- 11- A combined strategy should ideally be used to treat the upper and lower airway diseases in terms of efficacy and safety.

Introduction

Allergic rhinitis is clinically defined as a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membranes lining the nose. Symptoms of rhinitis include rhinorrhea, nasal obstruction, nasal itching and sneezing which are reversible spontaneously or under treatment. It is subdivided into "intermittent" or "persistent" disease (Table 1). The severity of allergic rhinitis can be classified as "mild" or "moderate-severe."

TABLE 1: Classification of allergic rhinitis

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| 1- "Intermittent" means that the symptoms are present: |
| • Less than 4 days a week, |
| • Or for less than 4 weeks. |
| 2- "Persistent" means that the symptoms are present: |
| • More than 4 days a week, |
| • And for more than 4 weeks. |
| 3- "Mild" means that none of the following items are present: |
| • Sleep disturbance, |
| • Impairment of daily activities, leisure and/or sport, |
| • Impairment of school or work, |
| • Troublesome symptoms. |
| 4- "Moderate-severe" means that one or more of the following items are present: |
| • Sleep disturbance, |
| • Impairment of daily activities, leisure and/or sport, |
| • Impairment of school or work, |
| • Troublesome symptoms. |

Previously, allergic rhinitis was subdivided, based on the time of exposure, into seasonal, perennial and occupational diseases (1-3). Perennial allergic rhinitis is most frequently caused by indoor allergens such as dust mites, moulds, insects (cockroaches) and animal danders. Seasonal allergic rhinitis is related to a wide variety of outdoor allergens such as pollens or moulds.

However, this is not entirely satisfactory as:

- There are some places where pollens and moulds are perennial allergens (e.g. grass pollen allergy in Southern California and Florida (4) or *Parietaria* pollen allergy in the Mediterranean area (5)).
- Symptoms of perennial allergy may not always be present all year round.
- The majority of patients are sensitised to many different allergens and therefore present symptoms throughout the year (6). In many patients, perennial symptoms are often present and patients present seasonal exacerbations when exposed to pollens or moulds.
- Many patients allergic to pollen are also allergic to moulds and it is difficult to define the pollen season (7).
- Due to the priming effect on the nasal mucosa induced by low levels of pollen allergens (8) and minimal persistent inflammation of the nose in patients with symptom free rhinitis (9), symptoms do not necessarily occur strictly in conjunction with the allergen season.

Thus, a major change in the subdivision of allergic rhinitis has been proposed in this document with the terms "intermittent" and "persistent". However, in the present document, the terms "seasonal" and "perennial" are still retained to enable the interpretation of published studies.

Allergic rhinitis is characterised by nasal obstruction, rhinorrhea, sneezing, itching of the nose and/or post-nasal drainage. It is often associated with ocular symptoms. Several other conditions can cause similar symptoms: infections, hormonal imbalance, physical agents, anatomical anomalies and the use of some drugs. Therefore, a detailed and correct aetiological diagnosis forms the basis for selecting optimal treatment.

Allergic rhinitis represents a global health problem. It is an extremely common disease worldwide affecting 10 to 25 % of the population (1, 10-12). However, this figure probably underestimates the prevalence of the disease, as many patients do not recognise rhinitis as a disease and therefore do not consult a physician (10). An increasing prevalence of allergic rhinitis over the last decades has been recognised (13, 14). Allergic rhinitis has been identified as one of the top ten reasons for visits to primary care clinics (15). Although allergic rhinitis is not usually a severe disease, it significantly alters the social life of patients (16, 17) and affects school learning performance (18, 19) as well as work productivity (20). Moreover, the costs incurred by rhinitis are substantial (21).

Other conditions associated with allergic rhinitis are asthma, sinusitis, otitis media, nasal polyposis, lower respiratory tract infection and dental occlusion. The cost of treating these conditions should be considered when evaluating the socio-economic impact of allergic rhinitis (22).

Asthma and rhinitis are common co-morbidities suggesting the concept of "one airway, one disease" (23). Rhinitis and asthma are linked by epidemiological, pathological and physiologic characteristics and by a common therapeutic approach (24-27). Although not universally accepted (28), the term "allergic rhinobronchitis" has been proposed to link the association between allergic asthma and rhinitis (29). Non-allergic asthma and rhinitis are also associated (30) but the mechanisms underlying the two diseases are not fully understood except, possibly, for aspirin-induced asthma (31). Moreover, costs for asthma are significantly increased in patients with allergic rhinitis (32). Patients with persistent allergic rhinitis should therefore be evaluated for asthma, and patients with asthma should be evaluated for rhinitis. A strategy combining the treatment of both upper and lower airway disease in terms of efficacy and safety appears to be optimal.

Clinical guidelines are systematically developed statements designed to help practitioners and patients make decisions about appropriate and effective health care (33). Guidelines have existed in various countries for decades and hundreds of them have been published for

many diseases (34) including asthma (35, 36) and allergic rhinitis (1-3, 37-40). There is considerable interest in guidelines as a tool for implementing health care based on proof of effectiveness. Guidelines should be informative, simple, easy to use and in a form that can be widely disseminated within the medical community in order to improve patient care. Unfortunately, many guidelines are not tested and may be difficult to use by non-specialists. Evidence-based medicine is an important method of preparing guidelines (41). Moreover, the implementation of guidelines is equally important.

New knowledge on the pathophysiological mechanisms underlying allergic inflammation of the airways has resulted in better therapeutic strategies. New routes of administration, dosages and schedules have been studied and validated. In addition, asthma co-morbidity should be well understood in order to achieve optimal treatment for patients.

The present document is intended to be a state-of-the-art for the specialist as well as for the general practitioner:

- to update their knowledge of allergic rhinitis,
- to highlight the impact of allergic rhinitis on asthma,
- to provide an evidence-based documented revision on the diagnosis methods,
- to provide an evidence-based revision on the treatments available,
- to propose a stepwise approach to the management of the disease.

The ARIA Paper is not intended to be a standard of care document for individual countries. It is provided as a basis for physicians and organisations involved in the treatment of allergic rhinitis and asthma in various countries to develop relevant local standard of care documents for their patients.

1- Classification

Rhinitis (rhinosinusitis) is classified as follows (Table 2). The differential diagnosis of rhinitis is presented in Table 3.

1-1- INFECTIOUS RHINITIS

Acute viral rhinosinusitis is one of the most common health complaints, affecting millions of people annually (42). It has been estimated that 0.5-2% of viral upper respiratory tract infections progress to an acute bacterial infection. Chronic rhinosinusitis affects 5-15% of the urban population (43) and thus exceeds the prevalence of many other chronic conditions (44). Four principal clinical types are recognised:

- acute,
- recurrent acute,
- chronic,
- acute exacerbations of chronic disease.

Attempts have been made to define these in terms of pathophysiology, microbiology, radiographic imaging, severity and duration of symptoms (45-47). This latter criterion has proved to be the most widely utilised, although, in the case of acute infectious rhinosinusitis, the accepted duration of symptoms may range from one day to less than twelve weeks (48-50).

In acute infectious rhinitis Rhinovirus, Influenza and Para-influenza, viruses are the most frequent initiators, whilst *Streptococcus pneumoniae* (20-35%) and *Haemophilus influenza* (6-26%) remain the most common bacteria (51). However, other agents including *Moraxella catarrhalis*, *Staphylococcus aureus* and anaerobic bacteria are also found.

The same bacteria are regarded as significant in chronic infectious rhinosinusitis where they are found in high titres from sinus aspirates. They may also cause acute exacerbations of the chronic disease. In conditions such as cystic fibrosis, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are regarded as important pathogens. In addition, many other bacteria may be encountered whose role is as yet undetermined (52). Fungi such as *Aspergillus* or the Dermatophyte fungi, *Alternaria*, *Bipolaris* or *Curvularia*, appear to be assuming greater importance (53-57). Other organisms such as *Mycobacterium tuberculosis*, *Klebsiella rhinoscleromatis*, *Mycobacterium leprae* and *Treponema pallidum* can also occur and both protozoan infection (leishmaniasis) and parasitic infection have been described.

Ciliary abnormalities, both congenital and acquired, immunodeficiency and direct trauma may all predispose individuals to the development of both acute and chronic infection (58-60).

1-2- ALLERGIC RHINITIS

Allergic rhinitis is subdivided into "intermittent", "persistent", "mild" and "moderate-severe" (Table 1).

TABLE 2: Classification of rhinitis

- Infectious
 - Viral
 - Bacterial
 - Other infectious agents
- Allergic
 - Intermittent
 - Persistent
- Occupational (allergic and non-allergic)
 - Intermittent
 - Persistent
- Drug-induced
 - Aspirin
 - Other medications
- Hormonal
- Other causes
 - NARES
 - Irritants
 - Food
 - Emotional
 - Atrophic
 - Gastroesophageal reflux
- Idiopathic

TABLE 3: Differential diagnosis of rhinitis

- Polyps
- Mechanical Factors
 - Deviated septum
 - Adenoidal hypertrophy
 - Foreign bodies
 - Choanal atresia
- Tumours
 - Benign
 - Malignant
- Granulomas
 - Wegener's Granulomatosis
 - Sarcoid
 - Infectious
 - Malignant - midline destructive granuloma
- Ciliary defects
- Cerebrospinal Rhinorrhoea

1-3- OCCUPATIONAL RHINITIS

Occupational rhinitis arises in response to an airborne agent present in the workplace and may be due to an allergic reaction or non-allergic hyperresponsiveness. Many occupational agents are irritant. Causes of occupational rhinitis include laboratory animals (rats, mice, guinea pigs, etc.), grains (bakers and agricultural workers), wood dust, particularly hard woods (mahogany, Western Red Cedar, etc.), latex and chemicals such as acid anhydrides, platinum salts, glues and solvents (61).

1-4- DRUG-INDUCED RHINITIS

A range of medications is known to cause nasal symptoms. These include:

- aspirin and other non-steroidal anti-inflammatory agents (NSAID). Aspirin intolerance is characterised by nasal secretion, eosinophilia, frequent occurrence of polyps, sinusitis, non-allergic asthma and usually by a good response to glucocorticosteroids (see chapter 3-3-2),
- reserpine (62),
- guanethidine (63),
- phenolamine,
- methyldopa,
- angiotensin converting enzyme (ACE) inhibitors (64),
- α -adrenoceptor antagonists,
- intra-ocular ophthalmic preparations such as β -blockers (65),
- chlorpromazine,
- oral contraceptives.

The term rhinitis medicamentosa (66, 67) applies to the rebound nasal obstruction which develops in patients who use intranasal vasoconstrictors chronically. Rhinitis medicamentosa can be a contributing factor to non-allergic non-infectious rhinitis, which may be the reason the patient uses the vasoconstrictor.

Cocaine sniffing is often associated with frequent sniffing, rhinorrhea, diminished olfaction and septal perforation (68, 69).

1-5- HORMONAL RHINITIS

Changes in the nose are known to occur during the menstrual cycle (70), puberty, pregnancy (71, 72) and in specific endocrine disorders such as hypothyroidism (73) and acromegaly. Hormonal imbalance may also be responsible for the atrophic nasal change in post-menopausal women.

Persistent hormonal rhinitis or rhino-sinusitis may develop in the last trimester of pregnancy in otherwise healthy women. Its severity parallels the blood oestrogen level. Symptoms disappear at delivery.

In women with perennial rhinitis, symptoms may improve or deteriorate during pregnancy (74).

1-6- OTHER CAUSES

1-6-1- Nasal symptoms related to physical and chemical factors

Physical and chemical factors can induce nasal symptoms which may mimic rhinitis in subjects with sensitive mucous membranes, and even in normal subjects if the concentration of chemical triggers is high enough (75, 76). Skier's nose (cold, dry air) (77) and gustatory rhinitis (hot spicy food) (78) have been described as distinct entities. However, the distinction between a normal physiological response and a disease is not clear; all rhinitis patients may exhibit an exaggerated response to unspecific physical or chemical

stimuli. Little information is available on the acute or chronic effects of air pollutants on the nasal mucosa (see chapter 3-2) (79).

1-6-2- Food-induced rhinitis

Food allergy is a very rare cause of isolated rhinitis (80). However, nasal symptoms are common among the many symptoms of food-induced anaphylaxis (80).

On the other hand, foods and alcoholic beverages in particular may induce symptoms by unknown non-allergic mechanisms.

Some spicy food such as red pepper can induce rhinorrhea, probably because it contains capsaicin. This is able to stimulate sensory nerve fibres inducing them to release tachykinins and other neuropeptides (81).

Dyes and preservatives as occupational allergens can induce rhinitis (82), but in food they appear to play a role in very few cases (80).

1-6-3- Eosinophilic rhinitis

Persistent non-allergic rhinitis with eosinophilia is a heterogeneous syndrome consisting of at least two subgroups: NARES and aspirin intolerance.

Non-allergic rhinitis with eosinophilia syndrome (NARES) was defined in the early 1980s (83, 84). Although it probably does not represent a disease entity on its own, it may be regarded as a subgroup of idiopathic rhinitis. It can be characterised by the presence of nasal eosinophilia and perennial symptoms of sneezing, itching, rhinorrhea, nasal obstruction and occasionally a loss of sense of smell in the absence of demonstrable allergy. It occurs in children and adults. Asthma is uncommon but approximately 50% of patients have non-specific bronchial hyperreactivity (85). NARES seems to evolve in three stages (86):

- migration of eosinophils from vessels to secretions,
- retention of eosinophils in the mucosa which might be linked to activation of unknown origin,
- nasal polyps.

It has been suggested that some NARES represent an early stage of aspirin-sensitivity (87).

NARES is not responsive to DSCG (88) but responds usually although not always to intranasal glucocorticosteroids (89).

1-6-4- Emotions

Stress and sexual arousal are known to have an effect on the nose probably due to autonomic stimulation.

1-6-5- Atrophic rhinitis

Primary atrophic rhinitis is characterised by progressive atrophy of the nasal mucosa and underlying bone (90), rendering the nasal cavity widely patent but full of copious foul-smelling crusts. It has been attributed to infection with *Klebsiella ozaenae* (91) though its role as a primary pathogen is not fully documented. The condition produces nasal obstruction, hyposmia and a constant bad smell (ozaenae). It must be distinguished from secondary

atrophic rhinitis associated with chronic granulomatosis conditions, excessive nasal surgery, radiation and trauma.

1-6-6- Gastroesophageal reflux

Gastroesophageal reflux can be associated with rhinitis, especially in children (92, 93).

1-7- Unknown aetiology (idiopathic rhinitis)

Otherwise sometimes termed "vasomotor rhinitis", these patients (usually females aged between 40-60 years) manifest an upper respiratory hyperresponsiveness to non-specific environmental triggers such as changes in temperature and humidity, exposure to tobacco smoke and strong odours.